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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,334	08/30/2001	Charles W. Rittershaus	TCS-411.1P US-1	9968

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	6

DATE MAILED: 07/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/943,334	RITTERSHAUS ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2001 and 08 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *28,29 and 37-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28,29 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 28, 29 and 37-39 are pending.

2. Applicant's election with traverse of tetanus toxoid as the species for helper T cell epitope portion of vaccine peptide in Paper No. 5 is acknowledged. The traversal is on the ground that vaccine peptide used in Applicants' claimed method in not just a single helper T cell epitope portion, such as one listed in Claim 29.

Applicant confirms that a vaccine peptide used in the claimed method for treating atherosclerosis do indeed comprises two distinct portions(a helper T cell epitope and B cell epitope) that are linked together. However, Applicant do not provide arguments showing that various helper T cell epitope portion of the vaccine peptide, which are derived from various antigenic peptides recited in Claim 29, are not patentably distinct or obvious variants.

In the previous Office Action (paragraph 4) it was stated that these different antigenic peptides are distinct species of helper T cell epitope portion of the claimed vaccine peptide, because their structure, physicochemical properties and mode of action are different. The examination of species would require different searches in the scientific literature and would involve the consideration of separate issues in determining patentability.

The species election requirement is still deemed proper and is therefore made FINAL.

Claims 28, 29 and 37-39 as they read upon elected species to a method for therapeutically or prophylactically treating atherosclerosis, comprising administrating a vaccine peptide, comprising a helper T cell epitope portion and B cell epitope portion, wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and B cell epitope portion comprises B cell epitope of CETP or method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and B cell epitope portion of CETP comprises a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1 or method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide wherein vaccine peptide comprises the amino acid sequence of SEQ ID NO:2 or dimer thereof are under consideration in the instant application.

2. The specification on Page 1 should be amended to update the status of the parent applications 08/432483 and 08/945289

3. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which Applicant may become aware in the specification.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112.

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 28 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A). It is improper to recite "A method for prophylactically treating atherosclerosis in human or other animal in need" in claim 28, line 1. According to Webster's dictionary "prophylactic" means "serving against or prevent". How can one prevent disease in said human or other animal that already has a disease?

B). It is improper to recite "The method for treating atherosclerosis according to claim 28" in claim 29, line 1. There is insufficient antecedent basis for this limitation in the claim 28. Preamble of Claim 28 recites "A method for therapeutically or prophylactically treating atherosclerosis."

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 28-29 and 37-39, are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, consisting of the amino acid sequence of SEQ ID NO:2 or a dimer thereof, does not reasonably provide enablement for: (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39. The specification does not enable any person skilled in

the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification does not enable one of skill in the art to practice the invention as claimed without undue experimentation.

There is insufficient guidance and direction how to use: (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39.

The specification does not provide sufficient guidance as to which method for therapeutically or prophylactically treating atherosclerosis, comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope of CETP, broadly encompass by the claims would have the same efficiency as method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, consisting the amino acid sequence of SEQ ID NO:2 or a dimer thereof. Furthermore, the term "comprising" is open-ended and in Claim 28 expands vaccine peptide to include additional non-disclosed amino acid sequences. It is not clear what portion of B cell epitope of CETP recited in claim 28, or what portion of carboxyl terminal region of human CETP, consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, recited in claim 37, have the same functional properties as portion of amino acid sequence of SEQ ID NO:2 from amino acid 16 to 31.

Furthermore, it is not clear what portion of a helper T cell epitope recited in claim 28, or what portion of various antigenic peptides, recited in claim 29, will have the same functional properties as portion of amino acid sequence of SEQ ID NO:2 from 1-15. A T cell epitope might contain protective and suppressive epitopes as taught by Etlinger (Immunol. Today, 13, 52-54, 1992). The effects of preimmunization through infection or vaccination must be evaluated. Epitope specific suppression occurs when animal is immunized with an antigen and then challenged with the antigen to which a hapten has been couples and the selective inhibition of anti-hapten response occurs. Because the mechanism of suppression is multifaceted and not well understood, it is unpredictable whether a particular sequence elicits help or suppression (see Etlinger pages 52-53).

Therefore, besides method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, consisting the amino sequence of SEQ ID NO: 2 or a dimer thereof, it is unpredictable if: (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39 will be effective in practicing the invention.

Colman *et al.* (Research in Immunology 145(1):33-36, 1994) teach single amino acid changes in an antigen can effectively abolish antibody antigen binding. Abaza *et al.* in Journal of Protein Chemistry (11(5):433-444, 1992) teach that single amino acid substitutions outside the antigenic site on a protein effect antibody binding. Further, Lederman *et al.* in Molecular Immunology (28:1171-1181, 1991) disclose that a single amino acid substitution in a common allele ablates binding of a monoclonal antibody (see entire document). Additionally, Li *et al.* in PNAS (77:3211-3214, 1980) disclose that dissociation of immunoreactivity from other biological activities when constructing analogs (see entire document).
Because of this lack of guidance, an undue experimentation would be required to determine which modifications in vaccine peptide would be acceptable to retain functional activity, and the fact that the relationship between the sequence of a protein/peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Ngo *et al.* in the Protein Folding problem and Tertiary Structure prediction, 1994, Merz *et al.*, (ed), Birkhauser, Boston, MA, pp.433 and 492-495), it would require an undue amount of experimentation for on of skill in the art to arrive at the claimed: (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising

administrating vaccine peptide comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39.

Moreover, the claimed invention in Claims 28-29 and 37-39 are drawn to a method of therapeutically or prophylactically treating atherosclerosis by administration vaccine peptide comprising helper T cell epitope portion and B cell epitope of CETP. Specification, while being enabling for method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, consisting the amino acid sequence of SEQ ID NO:2 or a dimer thereof, does not reasonably provide enablement for: (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification disclosure does not enable one skilled in the art to practice the invention with out an undue amount of experimentation.

At issue is whether or not the claimed method would function for "prophylactically treating of atherosclerosis". The nature of the invention is such that it would require the administration of vaccine peptide to prevent a mammalian subject from having atherosclerosis. However, according to Maillard et al (Presse. Med, 30, 73, 2201) there is lack in effective methods capable of preventing atherosclerosis-related conditions. (see Abstract)

The scope of the claimed (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39 is not commensurate with the enablement provided by the disclosure of method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, consisting the amino acid sequence of SEQ ID NO: 2 or a dimer thereof , with regard to the extremely large number of methods for therapeutically or prophylactically treating atherosclerosis, comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope of CETP broadly encompassed by the claimed invention.

Reasonable correlation must exist between the scope of the claims and scope of enablement set forth. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, and the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

7. Claims 28, 29 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The following *written description* rejection is set forth herein.

The term "comprising" is open-ended and in Claim 28 expands vaccine peptide to include additional non-disclosed amino acid sequences. It is not clear what portion of B cell epitope of CETP , recited in claim 28, or what portion of carboxyl terminal region of human CETP, consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, recited in claim 37, have the same functional properties as portion of amino acid sequence of SEQ ID NO:2 from amino acid 16 to 31.

Furthermore, it is not clear what portion of a helper T cell epitope recited in claim 28, or what portion of various antigenic peptides, recited in claim 29, will have the same functional properties as portion of amino acid sequence of SEQ ID NO:2 from 1-15.

Applicant is in possession of method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, consisting the amino acid sequence of SEQ ID NO:2 or a dimer thereof. Applicant is not in possession of : (A) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, as recited in claim 28; or (B) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide comprising *any* helper T cell epitope portion derived from an antigenic peptide selected from the group recited in claim 29 and *any* B cell epitope portion of CETP; or (C) method for therapeutically and prophylactically treating atherosclerosis comprising administrating *any* vaccine peptide, comprising *any* helper T cell epitope portion and *any* B cell epitope portion of CETP, comprising a carboxyl terminal region of human CETP consisting of between 6 and 26 consecutive amino acids of SEQ ID NO:1, as recited in claim 37; or (D) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising the amino acid of SEQ ID NO:2, as recited in claim 38, or (E) method for therapeutically and prophylactically treating atherosclerosis comprising administrating vaccine peptide comprising a dimer of the amino acid of SEQ ID NO:2, as recited in claim 39.

Consequently, conception in either case cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the method. Adequate written description requires more than a mere statement that it is part of the invention. The sequences themselves are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993).

A description of a genus of polypeptide sequences may be achieved by means of a recitation of a representative number of polypeptide sequences, defined by amino acid sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. Regents of the University of California v. Eli Lilly&Co., 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See University of California v. Eli Lilly and Co. 43 USPQ2d 1398.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 28-29 and 37-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1 989) in view of the known fact disclosed in the specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992).

The claims are examined as they read upon the elected species are drawn to a method for therapeutically treating atherosclerosis, comprising administrating a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid (residues 2-15 of SEQ ID NO:2) and B cell epitope portion comprises B cell epitope of CETP (between 6-26 consecutive amino acids of SEQ ID NO:1 or residues 16-31 of SEQ ID NO:2).

Whitlock et al., teaches that in vivo administration of CETP neutralizing antibodies leads to an elevation of circulating HDL, elevation in the ratio of circulating HDL to LDL, VLDL and total cholesterol, a decrease in the level of endogenous CETP activity and increase in the level of circulating HDL. Whitlock et al further teach that increase of HDL while decrease of VLDL would lead to decreased of LDL levels which would be beneficial for decrease in the development of atherosclerosis legions (see entire document and page 129 in particular).

The specification on page 2, lines 10-12, discloses that it is well known that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis .

The claimed invention differs from the prior art by the recitation of using a vaccine peptide comprising T cell epitope derived from Tetanus toxoid conjugated to a B cell epitope derived from C-terminus of CETP instead of using CETP neutralizing antibodies in a method for therapeutically treating of atherosclerosis.

Swenson et al. teaches the immunogenic peptide CETP-contains a B cell epitope and that administration of this peptide into animals results in production of anti- CETP antibody (see page 14319 in particular). Swenson et al. further teaches the criticality of the carboxyl terminal 26 amino acid sequences derived from CETP, for the elicitation of antibody which decrease the level of endogenous CETP activity (see abstract and entire document). The carboxyl terminal 26 amino acid sequence of CETP is 100 % identical to SEQ ID NO: 1 of the instant application. Thus, Swenson et al. teaches a immunogenic peptide that is the exact the same length and composition as amino acid sequence of SEQ ID NO:I and the same amino acid sequence as amino acid numbers 16-31 of SEQ ID NO:2. Swenson et al. also teaches that treating of atherosclerosis in human can be generally achieved by modulating the activity of endogenous CETP (see page 14318).

Stevens et al. teaches that active administration of antigen-tetanus toxoid conjugates to induce antibody responses for therapeutic effects are advantageous over passive administration of the antibody to the antigen because passive immunization procedures cause anti-antibody responses that cause serious side effect reaction upon repeated injection of the antibody (see column 2 in particular). In addition, Stevens et al. teaches adding a c-terminus cycteine onto the antigen so it can be linked to a Tetanus toxoid peptide or other carrier. Lastly, Stevens et al. teaches the conjugation of peptides to carriers to increase the peptides immunogenicity (see Abstract particular).

Valmori et al. teaches that universally antigenic T cell epitopes (a.a. 830-843 and 947-967) derived from Tetanus Toxoid (the elected T cell epitope) can be used as carriers (helper T cell epitope) for B cell epitope and that such hybrid peptides can be used to elicit antibody production in human and mice (see Abstract and entire document). Valmori et al. also teaches tetanus toxoid peptide that is the same as amino acids 2-16 of SEQ ID NO:2 of the instant application.

Giving the teaching of Stevens et al. and Valmori et al. that active administration of antigen-toxoid conjugates elicit antibody production in human and mice and teaching of Whitlock et al. that in vivo administration of CETP neutralizing antibodies leads to an inhibition of CETP activity and increase in the levels of circulating HDL and teaching of Whitlock et al., Swenson et al. and known fact disclosed in specification on page 2 that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis one ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to therapeutically treat atherosclerosis by administering a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein T cell epitope portion comprises a

helper T cell epitope derived from tetanus toxoid and B cell epitope portion comprises B cell epitope of CETP.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce a vaccine peptide comprising a helper T cell epitope portion derived from tetanus toxoid (as taught by Valmori et al. and Stevens et al.) and B cell epitope portion, comprising of carboxyl terminal 26 amino acid long CETP (as taught by Swenson et al) and use it in the method for therapeutically treating atherosclerosis because administration of such vaccine peptide would induce the generation of neutralizing antibody which would inhibit CETP activity (as taught by Whitlock et al.,) and inhibition of CETP activity would be essential in treating atherosclerosis (as taught by. Whitlock et al., the known fact disclosed in the specification on page 2 and Swenson et al).

One of ordinary skill in the art at the time the invention was made would have been motivated to create a vaccine comprising carboxyl terminal 26 amino acid long CETP –tetanus toxoid conjugate taught by the combined references of Swenson et al., Valmori et al. and Stevens et al. with the expectation that administration of such vaccine would elicit immune responses to the CETP component that would inhibit endogenous CETP activity in vivo. Inhibition of CETP activity would be expected to be useful in therapeutically treating atherosclerosis as taught by Whitlock et al. the known fact disclosed in specification on page 2 and Swenson et al.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

10. Claim 39 is are rejected under 35 U.S.C. 103(a) as being unpatentable over Whitlock et al. (J Clin. Invest.84:129,1989) in view of the known fact disclosed in specification on page 2, lines 10-12, Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992) and further in view of Talwar et al. (Proc. Natl. Acad. Sci, 91: 8532-8536 1994) or Stanton et al. (U.S. Patent NO: 5,807552).

The teachings of Whitlock et al. (J Clin. Invest.84:129,1989) , Stevens et al.(U.S. patent 6,143,305), Swenson et al (J. Biol. Chem. 264,14318, 1989) and Valmori et al. (J. Immunology 149: 717, 1992) have been discussed, supra.

The prior art teaching differ from the claimed invention only by recitation that vaccine peptide comprises a dimer of immunogenic peptide of SEQ ID NO:2.

Talwar et al. teaches the use of tetanus toxoid as a carrier to elicit immune responses to autoantigens such as human chorionic gonadotrophin. (see page 8532 and entire document). Talwar et al. also teach that peptide vaccine may also consists of a heterospicies dimer of the alpha-subunit of ovine luteinizing hormone and the beta-subunit of hCG conjugated to either of

two immunogenic carrier proteins to elicit production of autoantiboies, that specifically react with the particular endogenous protein.

Stanton et al. teaches the general advantage of vaccine, comprising multimers forms of immunogenic peptide over vaccine comprising monomer form of immunogenic peptide in both active and passive immunization (See Abstract and Column 8, line 20-25). Stanton et al. further teach that such vaccines are excellent candidates for providing immune protection for human and animals. (Column 8, line 24). Although Stanton et al. does not explicitly teaches a vaccine comprising a dimer form of immunogenic peptide, it would been obvious to one of ordinary skill in the art at the time the invention was made the advantage of using vaccine comprising more than one copy of immunogenic peptide for providing immune protection for human and animals.

Giving the teaching of Stanton et al. and Talwar et al. that vaccines comprising dimer of immunogenic peptide are excellent candidates for providing immune protection for human and animals and teaching of Stevens et al. and Valmori et al that active administration of antigen-toxoid conjugates elicit antibody production in human and mice plus teaching of Whitlock et al. that in vivo administration of CETP neutralizing antibodies leads to an inhibition of CETP activity and increase in the levels of circulating HDL and teaching of Whitlock et al., Swenson et al. and known fact disclosed in specification on page 2 that increase in the level of circulating HDL is essential in therapeutically treating of atherosclerosis one ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success to use a vaccine peptide, comprising a helper T cell epitope portion and CETP B cell epitope portion, wherein T cell epitope portion comprises a helper T cell epitope derived from tetanus toxoid and B cell epitope portion comprises B cell epitope of CETP in the method of therapeutically treating atherosclerosis

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to construct a vaccine comprising a dimer of immunogenic peptide which will providing immune protection for human and animals (as taught by Talwar et al. and Stanton et al.) wherein said immunogenic peptide comprising a helper T cell epitope portion derived from tetanus toxoid (as taught by Valmori et al.) and B cell epitope portion, comprising of carboxyl terminal 26 amino acid long CETP (as taught by Swenson et al) with the expectation that administration of such vaccine would induce the generation of neutralizing antibody which would inhibit CETP activity (as taught by Whitlock et al.,) and that inhibition of CETP activity would be essential in treating atherosclerosis (as taught by. Whitlock et al., the known fact disclosed in the specification on page 2 and Swenson et al).

One of ordinary skill in the art at the time the invention was made would have been motivated to create a vaccine which will providing immune protection for human and animals comprising a dimer of immunogenic peptide (as taught by Talwar et al. and Stanton et al.) wherein said immunogenic peptide comprising carboxyl terminal 26 amino acid long CETP –tetanus toxoid conjugate taught by the combined references of Swenson et al., and Valmori et al. with the expectation that administration of such vaccine would elicit immune responses to the CETP

component that would inhibit endogenous CETP activity in vivo. Inhibition of CETP activity would be expected to be useful in therapeutically treating atherosclerosis as taught by Whitlock et al. the known fact disclosed in specification on page 2 and Swenson et al.

11. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).
A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).
Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 28, 29 and 37-39 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 18 and 19 of U.S. Patent NO: 6,410,022

Although the confliction claims are not identical, they are not patentably distinct from each other because claim 18 of Patent NO: 6,410,022 is directed to method of treating atherosclerosis in human or animal comprising administering to the human or animal an antigenic vaccine hybrid peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises six to 26 consecutive amino acids of carboxyl terminal 26 amino acids of CETP. Claim 19 of Patent NO: 6,410,022 is directed to method of treating atherosclerosis in human or animal comprising administering to the human or animal an antigenic vaccine hybrid peptide comprising a universal helper T cell epitope portion linked to a B cell epitope portion, wherein said B cell epitope portion comprises six to 26 consecutive amino acids of carboxyl terminal 26 amino acids of human CETP, wherein antigenic vaccine hybrid peptide is a dimer.

12. No claims are allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is (703) 308-4232. The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703)

308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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July 20, 2002

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